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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/672,069	09/25/2003	Tariq M. Rana	UMY-062RCE	4721

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EXAMINER	
CHONG, KIMBERLY	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/672,069	RANA, TARIQ M.	
	Examiner	Art Unit	
	KIMBERLY CHONG	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4,19,21,22,27,33-36,39-63 and 84-108* is/are pending in the application.

4a) Of the above claim(s) *19,21,22,27,34-36,40-63 and 91-108* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,33,39 and 84-90* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 September 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 12/01/2008 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 05/29/2008 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on 12/01/2008, claims 1, 3, 4, 33, 39 and 84-90 are under examination and claims 19, 21-22, 27, 34-36, 40-63 and 91-108 are withdrawn from further consideration. Applicant has canceled claims 2, 5-18, 20, 23-26, 28-32, 37-38 and 64-83.

New Claim Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-4, 33, 39 and 84-90 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

To satisfy the written description requirement, MPEP §2163 states, in part "…a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention." Moreover, the written description requirement for a genus may be satisfied through sufficient description of a representative number of species by "…disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between functional and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus."

The instant claims are drawn to a small interfering RNA (siRNA) comprising a sense strand and an antisense strand wherein the antisense strand is complementary to the sense strand and has a sequence sufficiently complementary to a target mRNA, wherein the antisense strand and/or sense strand are modified such that in vivo stability is enhanced as compared to a corresponding unmodified siRNA and wherein the siRNA retains the ability to inhibit expression of the target mRNA by at least 30%.

The instant claims and specification fail to provide adequate written description of the entire genus of siRNA wherein the antisense strand and/or sense strand are modified such that in vivo stability is enhanced as compared to a corresponding

unmodified siRNA *and* wherein the siRNA retains the ability to inhibit expression of a target mRNA by at least 30%.

The specification, particularly in drawings 13A-D, illustrates siRNA wherein the strands are modified and wherein the siRNA retains the ability to inhibit expression of an EGFP target gene by at least 30%. The specification does not adequate written description for the entire genus comprising siRNA targeted to any target gene comprising any number of modified nucleotides that are capable of inhibiting the expression of said target gene by at least 30%. The skilled artisan would not know from the disclosure of siRNA targeted to EGFP that this siRNA is capable of inhibiting expression from any other target gene by at least 30%.

The specification as filed does not provide specific guidance that would lead one of skill in the art to the claimed invention. Furthermore, the state of the art cannot provide the specific guidance as evidenced by Holen et al. (Nucleic Acids Research 2002, Vol. 30, No. 8: 1757-1766 cited of IDS filed 11/20/07). Holen et al. teach that several siRNAs targeted against the same target gene demonstrated striking differences in silencing efficiency (see page 1757). The instantly claimed siRNA are not recognizable by their design that they are synthesized as capable of inhibiting the expression of any target gene by at least 30%. The instant specification nor the prior art provide the specific guidance to construct siRNA comprising modified nucleotides that are capable of silencing any gene expression by at least 30%.

MPEP §2163 states, in part "A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art

to immediately envisage the product claimed from the disclosed process." Because the prior art teach even siRNA synthesized to the same target gene demonstrate strikingly different degrees of gene silencing, one of skill in the art would not know which sequence of a broad genus of modified siRNA claimed targeted against any target would provide the necessary activity of silencing gene expression by at least 30% as compared to unmodified siRNA.

Moreover, MPEP §2163 states, in part: "[A] patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. A patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when … the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed. *In re Curtis*, 354 F.3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004).

Therefore, in the instant application, Applicants have not shown possession of the entire claimed genus of modified siRNA capable of silencing gene expression of a target gene by at least 30%.

Applicants are reminded that the written description requirement is separate and distinct from the enablement requirement. *In re Barker*, 559 F.2d 588, 194 USPQ 470 (CCPA 1977), cert. denied, 434 U.S. 1064 (1978); *Vas-Cath, Inc.* v. *Mahurkar*, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3, 4, 33, 39 and 84-90 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fosnaugh et al. (US 2003/0143732)

The instant claims are drawn to a small interfering RNA (siRNA) comprising a sense strand and an antisense strand wherein the antisense strand is complementary to the sense strand and has a sequence sufficiently complementary to a target mRNA, wherein the antisense strand is modified by the substitution of each uridine with 2'-fluoro uridine and each cytidine with a 2'-fluoro cytidine such that in vivo stability is enhanced as compared to a corresponding unmodified siRNA and wherein the siRNA retains the ability to inhibit expression of the target mRNA by at least 30% and wherein the siRNA further comprises a cleavage site for RISC and wherein the antisense strand is further modified by substitution of each adenosine and each guanosine located within 2 nucleotides upstream and 3 nucleotides downstream of the cleavage site with deoxy adenosine and deoxy guanosine.

For purposes of prior art, the claims are not drawn to a particular siRNA sequence nor is the claim drawn to a siRNA comprising any specific configuration of modified nucleotides and if given its reasonable broadest interpretation it is conceivable that the an siRNA sequence may not have uridines or cytidines and therefore may not

have modified uridines or cytidines. Further the limitation in claim 86 as amended reciting the substitution of each adenosine and guanosine located within 2 nucleotides upstream and 3 nucleotides downstream of the cleavage site referencing the antisense strand with a 2'-deoxy adenosine or guanosine wherein the siRNA comprises at least one 2'-deoxy adenosine or guanosine is also given its reasonable broadest interpretation. Therefore, because there is no specific sequence claimed and further no sequence claimed that indicates specifically what nucleotides are indicated as the cleavage site and because the specification on page 14 defines the cleavage site as 8-12 nucleotides from the 5' end of the antisense strand, the substitution of each adenosine or guanosine, depending on the sequence, could be from nucleotides 6 to 15 from the 5' end of the antisense strand. Essentially, substitution of just one adenosine or guanosine between nucleotides 6 to 15 of an antisense strand with a 2'-deoxy adenosine or guanosine would meet the limitations of claim 86. The following prior art rejection is based on this interpretation.

Fosnaugh et al. teach siRNA molecules comprising two strands of about 18 to 27 nucleotides in length wherein one or both strands can be chemically modified and comprises 2 nucleotide 3' overhang regions (see page 8, particularly paragraph [0056]). Fosnaugh et al. teach the siRNA molecules target and silence ADORA1 gene expression wherein expression of aberrant protein from said gene is involved in inflammatory diseases (see page 3). Fosnaugh et al. teach the antisense and/or the sense strand can comprise combinations of modified nucleotides such as 2' fluoro groups as well as 2'-deoxy groups and further specifically teach the pyrimidine groups

on a strand can comprise 2' fluoro groups (see at least page 7). On page 5, Fosnaugh et al. teach the introduction of chemically modified nucleotides provide a powerful means to overcome the limitations of in vivo stability and bioavailability inherent to native RNA molecules. Fosnaugh et al. teach the siRNA molecule has a cleavage site for RISC which mediates cleavage of the target gene and references the work of Elbashir et al. (EMBO 2002 also cited on IDS filed 02/27/2006) which identifies the cleavage region of siRNA. Fosnaugh et al. teach pharmaceutical compositions comprising said siRNA molecules 9see page 23).

Fosnaugh et al. do not specifically teach the siRNA comprising modified nucleotides retains the ability to inhibit expression of the target mRNA by at least 30% however on page 20 Fosnaugh et al. teach optimizing the activity of the siRNA comprising modified nucleotides to preserve the ability of the siRNA to mediate RNAi efficiently in cells. It would have been obvious to one of ordinary skill in the art to synthesize a siRNA comprising chemically modified nucleotides as taught above and optimize the incorporation of said modifications to obtain a siRNA with the highest ability to inhibit the desired gene expression.

Beginning in Example 1, Fosnaugh et al. teach detailed steps on constructing the said siRNA molecules and methods of testing the activity of said siRNA against the target gene. Given that Fosnaugh et al. teach the introduction of chemically modified nucleotides provides a powerful means to overcome the limitations of in vivo stability and bioavailability inherent to native RNA molecules, one would have clearly incorporated said modifications into a siRNA and would have optimized the position and

number of modified nucleotides to obtain a siRNA with the highest ability to inhibit the desired gene expression. Moreover, given that there are a multitude of general methods and strategies to determine the location of incorporation of chemically modified nucleotides as taught by Fosnaugh et al. (see page 20, particularly paragraph [0168]), one of ordinary skill in the art would have expected to be able to determine the location of incorporation of chemically modified nucleotides as instantly claimed while maintaining the siRNAs ability to inhibit gene expression by at least 30%.

Thus, the invention as a whole would have been prima facie obvious to one of skill in the art at the time the invention was made.

Response to Applicant's Arguments

Re: Claim Rejections - 35 USC § 103

The rejection of claims 1 and 86 under 35 U.S.C. 103(a) as being unpatentable over Tuschl et al. (WO 22/44321 of record), Eckstein et al. (U.S. Patent No. 5,672,695 of record), Parrish et al. (cited on IDS filed 02/25/2006) and Allerson et al. (US 2005/0026160) is withdrawn and therefore response to Applicant's argument is moot.

Re: Claim Rejections - 35 USC § 103

The rejection of claims 1, 3-4, 33, 39 and 84-90 under 35 U.S.C. 103(a) as being unpatentable over Tuschl et al. (WO 22/44321), Eckstein et al. (U.S. Patent No. 5,672,695) and Parrish et al. (cited on IDS filed 02/25/2006) is withdrawn and therefore response to Applicant's argument is moot.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Kimberly Chong/
Examiner
Art Unit 1635